INVITED LECTURE

CAN WE REVERSE NEGATIVE IMPACT OF PROLONGED MECHANICAL VENTILATION ON RESPIRATORY MUSCLES?

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Abstract

BACKGROUND: Prolonged mechanical ventilation although saving lives, can have decremental effect on repiratory muscles, mainly diaphragm. The aim of this article is to summarize the mechanisms of respiratory muscle atrophy and possible interventions for atrophy reversal.

Sažetak

UVOD: Dugotrajna mehanička ventilacija, iako spašava život, može imati negativan učinak na respiratorne mišiće, uglavnom dijafragmu. Cilj ovog članka je ukratko sažeti mehanizme atrofije respiratornih mišića i moguće intervencije za oporavak atrofije.Razrada: Sistematski pregled literature.Zaključak: U jedinici intenzivnog liječenja liječnici su svjesni negativnog utjecaja mehaničke ventilacije na plućni parenhim. No, u zadnje vrijeme sve više i više dokaza se pojavljuje, da mehanička ventilacija daje isuficijentni stres na respiratorne mišiće, a time se potiče i atrofija dijafragme i kontraktilna disfunkcije, što dovodi do produžene zavisnosti od mehaničke ventilacije. Istraživanja na životinjama su dokazala da neaktivnost dijafragme izaziva oštećenje i atrofiju mišićnih stanica. Studije na pacijentima na mehaničkoj ventilaciji potvrdile su navedenu pojavu i kod ljudi. Mehanizmi atrofije dijafragme su složeni i uključuju oksidativno oštećenje, smanjeni protok proteina, ekspresiju gena i staničnu signalizaciju te indukciju apoptoze mišićnih stanica dijafragme. Atrofija dijafragme i disfunkcija dovodi do produljene mehaničke ventilacije, zavisnosti od ventilatora i također do povećane smrtnosti.

Ova pojava može biti u nekih bolesnika preokrenuta s treningom respiratornih mišića. Rezultati između studija se razlikuju, uglavnom zato jer su korištene različite metode treninga respiratornih mišića, a uključeni su i pacijenti s različitim bolestima. Buduća istraživanja će pokazati koji pacijenti će imati najveću korist od treninga respiratornih mišića i koji režim treninga je najbolji za indukciju rasta mišića.

KLJUČNE RIJEČI: dijafragma, respiratorni mišići, mehanička ventilacija, slabost dijafragme, inspiratorni trening mišića, respiratorna fizioterapija

Discussion

Systematic literature review.

CONCLUSIONS: Intensive care unit physicians are aware of negative impact of nechanical ventilation on lung parenchyma. But recently more and more evidence is accumulating, that mechanical ventilation provides isufficient stress on respiratory muscles and with that promoting diaphragm atrophy and contractile dysfunction which leads to prolonged weaning and ventilator dependency. Research on animals has documented that inactivity of diaphragm induces injury and atrophy of muscle cells. Studies on patients on controlled mechanical mentilation confirmed this phenomena in humans. The mechanisms of diaphragm atrophy are complex an include oxidative injury, decreased protein turnover, gene expresson and cell signaling, and induction of diaphragm muscle cell apoptosis. Diaphragm atrophy and dysfunction leads to prolonged mechanical ventilation, ventilator dependency and also to increased mortality.

This phenomena can be in some patients reversed with respiratory muscle training. The results between studies vary, mainly beacuse in they used different methods of respiratory muscle training, and included the patients with different diseases. Future studies will show which patients will have the greatest benefit from respiratory muscle trainig and which trainig regime is best for muscle growth induction.

KEYWORDS: diaphragm, respiratory muscles, mechanical ventilation, diaphragm weakness, inspiratory muscle training, respiratory physiotherapy

Introduction

Mechanical ventilation is a life saving procedure for patients with respiratory failure. There are two main mechanisms with which mechanical ventilation helps reversing respiratory failure. It decreases work of breathing - this is the main mechanism in obstructive lung diseases and neuromuscular diseaes and helps to improve oxyegenation through better ventilation/perfusion matching and alveolar recruitment – for example in acute distress respiratory syndrom (ARDS) and lung infections (1).

The Intensive care unit (ICU) physicians were aware of harmful effects of mechanical,ventilation on lungs (2,3), and in this knowledge has lead to specific protocols for mechanical ventilation in patients with ARDS to minimize ventilator induced lung injury

When the disease which caused the respiratory failure is cured, it is time to discontinuate ventilator support. Not all patients are capable of weaning from mechanical ventilation – up to 30% of them will experience weaning problems (4) and weaning from mechanical ventilation account up to 60% of the total ventilation time (5). But not all patients are capable of weaning, up to 3% of the become ventilator dependent, which is a huge burden for society and families involved (6).

There are diseases that have direct influence on respiratory muscles, but investigators have postulated that mechanical ventilation per se, though live saving procedure, can damage repiratory muscles as well (7). This injury is the main cause of mechanical ventilation weaning failure in many patients. Unfortunately our understanding of ventilator induced respiratory muscle weakness is still very limited and future studies will be neccesary to identify procedures for prevention and treatmend of ventilator induced respiratory muscle weakness. Physicians should not assume that respiratory muscle weakness in a ventilated patient is diagnostic of ventilator-induced muscle injury. While ventilator injury is one possibility, numerous other common conditions, including sepsis and the administration of antibiotics, corticosteroids, sedatives and neuromuscular agents, can also induce respiratory muscle weakness and should be taken into account.

There are some known mechanisms of ventilator induced respiratory muscle weakness - some from animal studies and other from patient studies. Some of pathophysiologyical mechanisms are also known – majority of them from animal models, but patient studies are increasing in number and our knowledgeof the problem is rapidly increasing.

Discussion

Animal models of ventilator induced muscle injury

There were many studies of mechanical ventilation influence on repiratory muscles in animals during last twenty years. One of them showed, that 11 days of controlled mechanical ventilation produced a 46% decrease in respiratory muscle strength (8). In that study, animals received neuromuscular blocking agents to ensure that they made no respiratory efforts; which is different from the more commonly employed mode, assist-control ventilation, where patients continue to make some respiratory efforts in addition to receiving assistance from the ventilator (9).

Other studies have revealed that complete cessation of diaphragmatic activity with controlled mechanical ventilation – alone (10) or in combination with neuromuscular blocking agents (11) – results in injury and atrophy of diaphragmatic fibers. Muscle fibers generate less force in response to stimulation, not just because of their decreased bulk but even when normalized for cross-sectional area. The decrease in diaphragmatic force ranges from 20% to more than 50%. The alterations in muscle function occur rapidly, within 12 hours of instituting mechanical ventilation (12), and they appear to increase as ventilator duration is prolonged (13).

The degree of muscle injury depends of ventilator settings. Assisst-control mode of mechanical ventilation which preserves some of the spontaneous breathing appears to preserve the impairment of diaphragmatic contractility, but complete repiratory support with inactive repiratory muscles leads to 48% decrease in contractility (14). Even some intermittent bursts of unasissted breathing can limit ventilator induced injury (15).

The role of high positive end expiratory pressure (PEEP) in ventilator induced respiratory muscle injury remains to be discovered. It is documented that limb immobilization (with a cast) in a shortened position - which is exactly the same PEEP does with a diaphragm - accelerates protein degradation and causes myonuclear apoptosis (16). If high PEEP has any influence on the diaphragm atrophy remains to be discovered.

Evidence for ventilator induced muscle injury in humans

Almost ten years old study (17) presented human data that support the findings of the animal studies. They obtained biopsies of the costal diaphragms from 14 brain-dead organ donors. These patients exhibited diaphragmatic inactivity and had received mechanical ventilation for 18 to 69 hours. They also obtained intraoperative biopsies of the diaphragms of 8 patients undergoing thoracic surgery for suspected lung cancer; these control patients had experienced diaphragmatic inactivity and mechanical ventilation for 2 to 3hours.

Histologic measurements revealed marked diaphragmatic atrophy in the brain-dead patients. Compared with the control group, the mean cross-sectional areas of muscle fibers were significantly decreased by more than 50%. The cross-sectional area of fibers of the pectoralis major, a muscle not affected by mechanical ventilation, was equivalent in the two groups. This finding indicates that the diaphragmatic atrophy experienced by the brain-dead patients was not part of some generalized muscle-wasting disorder.

Other human data support the likelihood that mechanical ventilation can induce respiratory muscle atrophy. Knisely et al (18) performed autopsies in 13 infants who died after receiving mechanical ventilation for ≥12 days and 26

infants who died after ventilation for ≤7 days. The cross-sectional areas of diaphragmatic fibers were much smaller in the infants who received the longer duration of mechanical ventilation. Fibers taken from strap and tongue muscles were similar in the two groups.

There are many intra and intercellular pathophysiological mechanism that can cause ventilator induced respiratory muscle injury and are induced by controled mechanical ventilation. Some are from animal and other from human studies. Here is a quick review of them.

Mechanical ventilation induced diaphragmatic atrophy

When the patients are ventilated in a controlled mechanical ventilation mode (CMV) there is a rapid onset of the diaphragm atrophy, which was documented in several animal models (19-24). In those studies just 12 to 18 hours of CMV resulted in significant atrophy of diaphragmatic muscle in contrast to limb muscles, which achieved the same level of atrophy after 96 hours of inactivity. This showed that diaphragmatic atrophy is extremly rapid and even exceeds atrophy induced by denervation (25). Similar studies confirmed the same mechanism in humans (26)

Mechanical ventilation induced changes in diaphragm miscle fibers ultrastructure

Animal studies revealed that CMV changes the ultrastructure of diaphragmatic muscle fibers, which is different than in limb muscles, where no such changes were found (27). Prolonged CMV induces myofibrilar disarray and alternations in Z line structure in diaphragmatic muscle fibers. It increases number of cytoplasmic lipid vacuoles whose role is unclear.

Mechancal ventilation induced contractile dysfunction

Numerous studies in animal models showed that CMV promotes diaphragmatic contractile dysfunction (27, 28, 29). Prolonged CMV promotes progressive decrease in diaphragmatic specific force production in submaximal and maximal stimulation frequencies (30). This phenomena is evem more important in older patients, beause aging itself also impairs contractile function of the diaphragm (31).

Mechanical ventilation induced change in protein turnover

Prolonged CMV depresses diaphragmatic protein synthesis and accelerates protein breakdown (32). This phenomena is expressed throuhout the entire time on CMV and it is mediated through activation of proteoliytic enzymes, namely calpain, caspase-3 and ubiquitin proteasome system (21, 12).

Mechanical ventilation induced oxidative stress

CMV lasting more than 6 hours results in diaphragmatic redox disturbances and it is demostrated as increases in markers of oxidative injury (21, 33, 34). This redox disturbances occurs because prolonged CMV inceases reactive oxygen species (ROS) production and diminished antioxidant properties of the diaphragm (34). Prevention of oxidative stress may protect the diaphragm against atrophy and contractile dysfunction.

Mechanical ventilation induced changes in gene expression and cell signalling

Prolonged CMV changes the expression of many genes in diaphragm muscle fibers. It induces production of proteolytic enzymes , down regulates genes involved in energy metabolism (35) and calcium homeostasis (36). It induces genes promoting muscle atrophy (37) and changes expression of several myogenic regulatory factors (36).

Prevention and treatment of mechanical ventilation induced respiratory muscle atrophy

The main mechanism of mechanical vetilation induced respiratory mucscle atrophy is limiting use of CMV. There are modes of mechanical ventilation which enable at least partial spontaneous breathing and it should be used as soon as there is no need for CMV mode. It appears that ventilation modes that offer just partial support of breathing reduce ventilator induced respiratory muscle atrophy (38). Just short periods of spontaneous breathing (5 min) could retard many if not all effects induced by CMV (15).

Surprisingy glucocorticiod treatment, which is associated with steriod induced myopathy, seems to protect the diaphragm from harmful effects of controlled mechanical ventilation (39).

Burt some of the patients are not able or alloved to breathe spontaneously for a longer period of time – head injury, ARDS patients for example. In those patients all harmful effect of controlled mechanocal ventilation show in their full might. Those patients are usually difficult to wean from ventilator and represent signficant personell and financial burden for any ICU unit.

Conclusion

The solution probably lies in the hands of respiratory physiotherapists. In a review from 2015 Elkins and Dentice made a systematic review of articles about inspiratory muscle training. The results were very heterogeneus – mainly because of different criteria for patient selection, training methods and load applied during trainig. The most importand message from this study is, that inspiratory muscle trainig works, it improves weaning succes and it has the potential for shortening ICU stay. For more conclusive result studies should be better designed – with better patient selection (comparable diseases that lead to respiratory failure) and with clear training and weaning protocols (40).

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